Double-Intensive Therapy in High-Risk Multiple Myeloma

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A high remission rate is achieved with high-dose melphalan (HDM) in multiple myeloma (MM), and autologous transplantation of hematopoietic stem cells allows a prompt hematologic recovery after high-dose therapy. We treated 97 patients with high-risk MM (group 1: 44 advanced MM including 14 primary resistances and 30 relapses; group 2: 53 newly diagnosed MM) with a first course of HDM. For responding patients a second course of high-dose therapy with hematopoietic stem cell support was proposed. After the first HDM, the overall response and complete remission rates were 71% and 25% with no significant difference between the two groups. The median durations of neutropenia and thrombocytopenia were significantly longer in group 1 (29.5 days and 32 days, respectively) than in group 2 (23 days and 17 days, respectively). This severe myelosuppression led to eight toxic deaths and to the fact that only 38 of the 69 responders could proceed to the second course (three allogenic and 35 autologous transplantations). Among the 35 patients undergoing autologous transplantation (10 in group 1, 25 in group 2), 31 received their marrow unpurged collected after the first HDM, and four received peripheral blood stem cells. The median durations of neutropenia and thrombocytopenia after autologous transplantation were 24 days and 49 days, respectively. Two toxic deaths and nine prolonged thrombocytopenias were observed. The median survival for the 97 patients was 24 months (17 months in group 1, 37 months in group 2) and the median duration of response was 20 months. The only parameters that have a significant impact on the survival are the age (±50 years) and the response to HDM. The median survival of the 35 patients undergoing autologous transplantation is 41 months, but the median duration of remission is 28 months with no plateau of the remission duration curve. Patients responding to HDM may have prolonged survival, but even a second course of high-dose therapy probably cannot eradicate the malignant clone.

IN THE LAST few years, high-dose therapy has been introduced in the management of multiple myeloma (MM). In 1983, McElwain and Powles[1] treated nine patients with high-dose melphalan (HDM) and obtained three complete remissions (CR). This preliminary experience was amplified, and Selby et al[2] published updated results on 58 patients. The conclusion of this study was that a high CR rate could be achieved with HDM, but it would be at the expense of a severe myelosuppression with a high toxic death rate. However, the median duration of remission was only 19 months.

Autologous bone marrow transplantation (ABMT) is another approach of high-dose therapy. Barlogie et al[3] have shown that the duration of neutropenia was shorter and the incidence of serious infections lower in patients receiving an autologous bone marrow support. The same investigators have also shown that ABMT allows a prompt hematopoietic recovery after a myeloablative treatment, such as the combination of HDM and total body irradiation (TBI).[4]

We tried to combine these two modalities of high-dose therapy in young patients with poor prognosis MM. The objectives of the first course of HDM, performed without any hematopoietic support, were to achieve a high tumor cell mass reduction and an in vivo purging of the marrow before the second course. The second course was followed by the reinfusion of hematopoietic stem cells collected during chemoinduced remission. The objective of this second course was to maintain the remission obtained by the first course.

The preliminary report on two patients was encouraging,[5] and we present here the updated data concerning 97 patients.

MATERIALS AND METHODS

Patients

From April 1984 to July 1990, 97 patients less than 70 years old and treated in nine French centers received at least one course of HDM for poor-prognosis MM. Two groups of patients were analyzed.

Group 1: Advanced MM. This group consisted of 44 patients either primarily refractory to at least two protocols of conventional chemotherapy, including the VAD regimen[6] (14 patients), or in relapse (30 patients). Relapses were further divided into the following: sensitive to standard-dose chemotherapy (5 patients), untested (14 patients), or resistant (11 patients).

Group 2: Newly diagnosed MM. In this group of 53 patients HDM was administered as part of frontline therapy, either after one to three cycles of debulking chemotherapy or to patients responding to their first conventional treatment regimen. Only two patients did not receive debulking treatment before HDM.

The initial characteristics of the patients are shown in Table 1.

The study was approved by the Institutional Review Board. Informed consent was obtained in each case according to the Declaration of Helsinki.

First Course of HDM

Melphalan was administered by 30-minute infusion with a forced saline diuresis as previously described.[1] Eighty-four patients received 140 mg/m^2 melphalan. Patients with a glomerular filtration rate under 40 mL/min were not included, and patients with a glomerular filtration rate between 40 and 50 mL/min received a lower dose of HDM (60 to 120 mg/m^2). Thus, 12 patients (nine in group 1, three in group 2) received lower doses of melphalan (120 mg/m^2 five patients, 100 mg/m^2 two patients, 80 mg/m^2 four patients, 60 mg/m^2 one patient) either because of their age, physical appearance, or impaired renal function. One patient with refractory MM was treated with 100 mg/m^2 melphalan on 2 consecutive days. Eighty-three patients (89%) were treated in

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Table 1. Clinical Characteristics of the Patients

	All	Group 1 Advanced MM	Group 2 Newly Diagnosed MM
No. of patients	97	44	53
Sex	57/40	20/24	37/16
Age (median)	26-67 (51)	29-67 (51)	26-67 (51)
Type of myeloma* (IgG/IgA/BJ)	48/23/24	21/9/12	27/14/12
κ/λ	65/30	32/10	33/20
Initial DS stage	2/8/87	1/6/37	1/2/50
Initial β2 microglobulin mg/L (median)	1.5-25 (3.3)	1.7-25 (3.9)	1.5-16 (3.3)
No. of previous protocols	1-5	1-5	0-2
No. of previous chemotherapy cycles (median)	0-65 (4)	3-65 (14)	0-9 (2)
Prior radiotherapy (%)	19 (19.5)	12 (27)	7 (13)
No. of patients pretreated with anthracyclines (%)	52 (53.5)	35 (79.5)	17 (32)
Interval diagnosis-HDM (median in mo)	0-95 (5.5)	2-45 (23)	0-43 (2)
Interval first treatment-HDM (median in mo)	0-91 (4.5)	0-91 (19)	0-10 (2)

Abbreviation: DS, Durie-Salmon.
*Two nonsecreting MM.

laminar airflow rooms with total gut decontamination. Antibiotics and transfusions were used as indicated in each center. Patients were categorized according to the M component, the Durie-Salmon staging,[7] and the β2 microglobulin level (only in 49 patients, 16 in group 1, 33 in group 2).

Response to HDM was assessed following the criteria defined by Gore et al.[8] Patients were regarded as having achieved CR when no paraprotein was measurable by serum proteins electrophoresis, when no Bence Jones proteinuria was detectable on urine electrophoresis, and when bone marrow aspiration showed less than 5% plasma cells. In the majority of cases the absence of paraprotein was confirmed by immunofixation. Patients were in partial remission (PR) if there was a 50% decrease in M component or bone marrow infiltration. All other results were regarded as failures.

Marrow Collection and BMT

In the first part of the study (before 1987), marrow was collected and cryopreserved only in patients achieving CR after HDM. After the publication by Barlogie et al[4] showing the feasibility of ABMT with marrow contaminated with up to 30% of plasma cells, marrow was also collected in patients achieving PR. Marrow was not purged in vitro. In four cases, peripheral blood stem cells were collected instead of marrow.

The preparative regimen to autologous transplantation was a second course of 140 mg/m^2 HDM alone in the first 18 patients. As the tolerance of this procedure was good, the following 17 patients received a myeloablative conditioning regimen with high-dose chemotherapy (140 mg/m^2 melphalan or 120 mg/k cyclophosphamide) plus TBI (16 patients) or the Baltimore regimen busulfan-cyclophosphamide[9] (one patient previously treated by radiation). TBI was administered at a dose of 12 Gy in six fractions in 12 cases and 10 Gy single dose in four cases.

Statistical Analysis

Actuarial curves were plotted from the date of the first course of HDM following the Kaplan-Meier method.[10] Differences between the curves were analyzed with the log-rank test.[11] Overall survival was defined as the time from first HDM to death. Progression-free survival (PFS) was evaluated from the time of remission achievement (CR or PR) after the first course of HDM until relapse. Relapse was assessed according to criteria defined by Mandelli et al[12]: 25% increase in the serum paraprotein, increase in the urinary paraprotein level to more than 2 g per day, reappearance of the paraprotein in serum or urine (for complete responders), increase in the size or number of lytic bone lesions.

The following parameters were analyzed for their impact on the clinical outcome (CR and overall response rates, survival and PFS): sex, age at the date of HDM, heavy- and light-chain isotype, initial β2 microglobulin level ($\leq$3 mg/L or $>$3 mg/L), response to conventional chemotherapy in group 1 (sensitive and untested relapses versus primary resistances and resistant relapses), interval between the diagnosis or the start of conventional treatment and the date of HDM ($\leq$5 and 12 months, $>$5 and 12 months), number of conventional protocols and number of chemotherapy courses administered before HDM, and prior radiotherapy. Response rates were compared by the chi-squared test. Nonparametric values were compared by the Wilcoxon rank-sum test.[13] Correlation studies were based on the Spearman rank correlation coefficient.[14]

RESULTS

Results of the First Course of HDM

After the first course of HDM, the overall response rate was 71% (69 of the 97 patients): 24 patients achieved CR (25%), 45 had PR (Table 2). It should be noted that of these 45 PR, 24 were very good PR with less than 5% plasma cells in the marrow and at least 90% reduction of the M component. There were 28 failures, including eight (8%) toxic deaths. The results were better in group 2 (75.5% responses and 28% CR) than in group 1 (66% responses and 20.5% CR), but these differences are not significant. In group 1, both CR and response rates were higher in 19 untested or sensitive relapses than in 25 resistant MM (37% and 84%, respectively, *v* 8% and 52%). The results were very poor in the group of resistant relapses with no CR and only 5 responses out of 11 patients. Among the parameters tested for their influence on the response rate, age was the only significant one. Patients 50 years old or less had an 83% response rate versus 62% for patients over 50 years ($P = .036$). The CR rate was lower in IgG than in non-IgG MM (23% *v* 51%, $P = .008$), but heavy chain isotype had no influence on the overall response rate (67% *v* 75.5%, $P = .42$).

Toxicity of the First Course of HDM

The median duration of neutropenia ($<0.5 \times 10^9$/L) was 24.5 days (range 11 to 180 days) and was longer in

Table 2. Clinical Outcome of the 97 Patients Receiving at Least One Cycle of Intensive Therapy

	No. of Patients	Results of the First HDM			Median Survival (mo)
		CR	CR + PR	Failure	
Total (%)	97	24 (25)	69 (71)	28	24
Group 1 (%) (advanced MM)	44	9 (20.5)	29 (66)	15	17
Group 2 (%) (newly diagnosed)	53	15 (28)	40 (75.5)	13	37
Age (yr)					
≤ 50	42	10	35 } $P = .036$	7	42 } $P = .009$
> 50	55	14	34	21	18
Type of myeloma					
IgG	48	5 } $P = .008$	32	16	50+ } $P = .06$
Non-IgG	49	19	37	12	19
Response to previous therapy					
Sensitive or untested relapse	19	7 } $P = .048$	16 } $P = .056$	3	17.5
Resistant	25	2	13	12	14
Resistant relapse	11	0	5	6	7
Primary resistanse	14	2	8	6	23.5

group 1 than in group 2 (29.5 days *v* 23 days, $P = .005$) (Table 3, Fig 1A). The median duration of thrombocytopenia was 18.5 days and was also longer in group 1 than in group 2 (32 days *v* 17 days, $P = .03$) (Fig 1B). Eighteen patients in group 1 and seven in group 2 experienced very prolonged myelosuppression (more than 30 days). One patient in group 1 could never have a hematopoietic reconstitution and finally died of a fungal infection. As a result of this severe hematologic toxicity, 55 patients had at least one episode of documented bacteriemia (26 in group 1, 29 in group 2) and 25 had at least one clinically documented infection (11 in group 1, 14 in group 2). The median number of platelet transfusions was seven (range 0 to 52), with no significant difference between the two groups. Eight patients died of infectious complications of neutropenia (three in group 1, five in group 2). As the myelosuppression was significantly more severe in group 1, the correlation between the duration of neutropenia and the pretreatment characteristics was analyzed in this group. None of these parameters was significantly correlated to the duration of neutropenia.

Table 3. Toxicity of the First Course of HDM

	All	Group 1 (advanced MM) N = 44	Group 2 (newly diagnosed MM) N = 53
Dose of HDM mg/m² (median)	60-200 (140)	60-200 (140)	80-140 (140)
No. of patients treated with 140 mg/m²	80	32	48
Duration of neutropenia (median)	11-180 (24.5)	12-180 (29.5)	11-73 (23)
Duration of thrombocytopenia (median)	1-240 (18.5)	6-240 (32)	1-102 (17)
No. of patients with aplasia longer than 30 d (%)	25 (26)	18 (41)	7 (13)
No. of patients with documented bacteriemia (%)	55 (57)	26 (59)	29 (55)
No. of patients with clinically documented infection (%)	25 (26)	11 (25)	14 (26)
No. of toxic deaths (%)	8 (8)	3 (7)	5 (9.5)

Survival

The median follow-up time for living patients is 32 months (9 to 68 months). The median survival for the entire group of 97 patients is 24 months with a 26% ± 9% probability of being alive at 5 years (Fig 2). The corresponding figures are, respectively, 17 months and 15% ± 11% at 4 years in group 1, 37 months and 28.5% ± 13% at 5 years in group 2. However, the actuarial survival curves are not

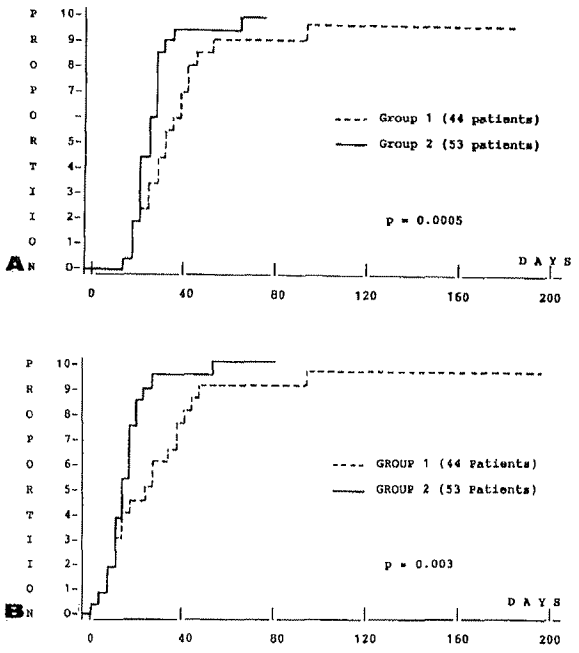

Fig 1. Duration of neutropenia (A) and of thrombocytopenia (B) after the first course of HDM. Comparison between group 1 (advanced MM) and group 2 (newly diagnosed MM). Kaplan-Meier plots, log-rank test (A), $P = .0005$; (B), $P = .003$.

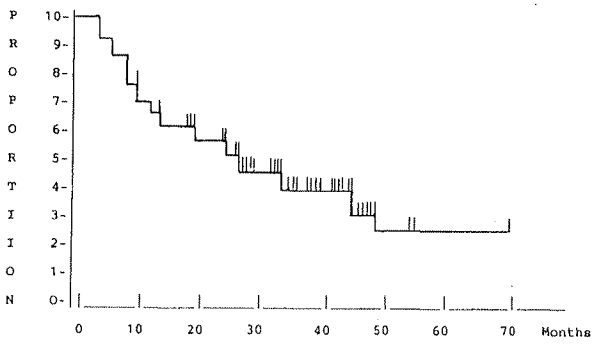

Fig 2. Overall survival of the 97 patients having received at least one course of HDM.

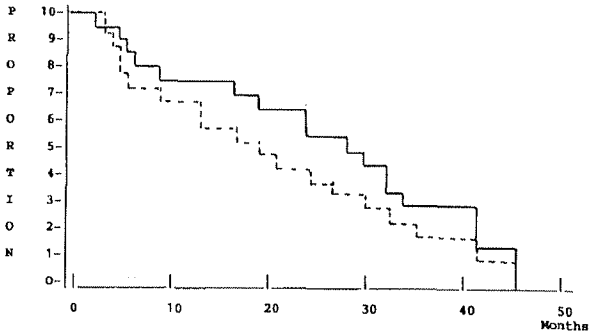

Fig 4. Duration of remission in the 69 patients responding to HDM (——) and in the 35 patients undergoing autologous transplantation (—).

statistically different ($P = .16$) (Fig 3). The PFS was evaluated in the 69 responding (CR + PR) patients (Fig 4). Forty-eight of the responders relapsed within 45 months and the median duration of response was 20 months with no significant difference between group 1 (18 months) and group 2 (23.5 months).

In univariate analysis, sex, light-chain isotype, β2 microglobulin level, interval between diagnosis or start of initial treatment and date of HDM, number of standard dose protocols and number of chemotherapy courses administered before HDM, prior radiotherapy had no significant impact on the survival and PFS rates. Only the age and the response to HDM appear to be of significant value. The median survival was 42 months for patients under 50 years old and 18 months for patients over this limit, and the survival curves differ significantly ($P = .009$) (Fig 5A). The median survival was 28 months for the 69 responders to the first course of HDM, and only 7 months for the 28 nonresponders ($P = .02$) (Fig 5B). There is a trend in favor of a longer survival for patients with IgG MM, but the difference does not reach statistical significance by the log-rank test ($P = .06$).

The Second Course of High-Dose Therapy

Of the 69 responders to HDM, 35 proceeded to autologous transplantation (51% of the responders and 36% of the entire group). Three patients less than 45 years old and with an HLA-identical sibling underwent allogenic BMT. The other 31 patients could not receive a second course of high-dose therapy for a variety of reasons (relapse 10, poor hematologic recovery or heavy marrow contamination 7, poor clinical status 8, severe fungal infection 3, patient's refusal 3). The exclusion rate was higher in group 1 (18 of 29 responders) than in group 2 (13 of 40 responders). Eleven of 44 patients (25%) were transplanted (1 allogenic, 10 autologous) in group 1 and 27 of 53 (51%) in group 2 (2 allogenic, 25 autologous). Of the three allogenic BMTs, one was in group 1 and was transplanted in PR after the first course of HDM. The other two were in group 2 and both were transplanted in PR. All three patients died, one of graft-versus-host disease at day 45 post BMT, one from interstitial pneumonitis 5 months after BMT, and one from bacterial sepsis in apparent CR after 15 months.

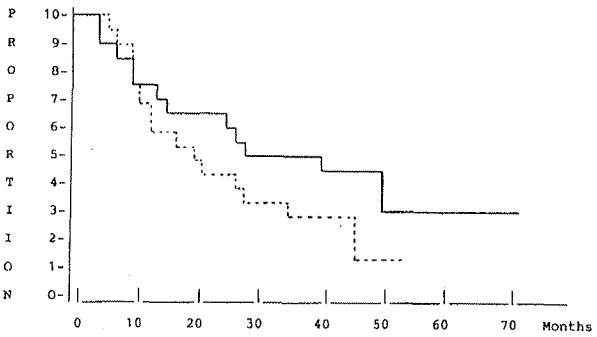

Fig 3. Comparison of the survival curves between advanced MM ([---], group 1, N = 44) and newly diagnosed MM ([—], group 2, N = 53) ($P = .16$).

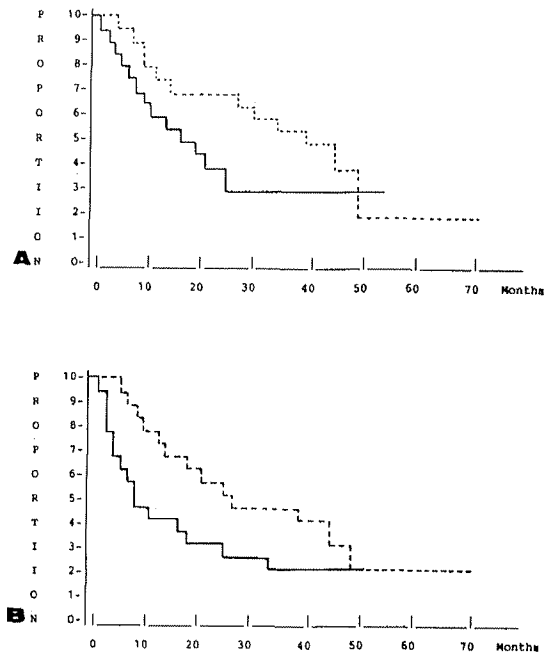

Fig 5. Prognostic factors. Influence of the age (A: [---], age ≤ 50 years [N = 42]; [—], >50 years [N = 55]) and of the response to the first course of HDM (B: [---], responders to HDM [N = 69]; [—], nonresponders, to HDM [N = 28]) on the survival. (A), $P = .009$; (B), $P = .02$.

Of the 35 patients undergoing autologous transplantations (10 in group 1 and 25 in group 2), 12 were in CR 22 in PR and 1 in early relapse at the time of transplant.

The median interval between HDM and marrow collection was 3 months (1.5 to 19 months). In one patient, peripheral blood stem cells were collected 2 months before the first HDM after one course of conventional chemotherapy. The percentage of reinfused plasma cells ranged from 0 to 30 (median 1). In 22 cases, the marrow contained less than 5% plasma cells. The median interval between the first HDM and autologous transplantation was 5 months (2 to 23). Only 14 patients were transplanted within 4 months after the first HDM. The median duration of neutropenia was 24 days and the median duration of thrombocytopenia was 49 days (Fig 6). Prolonged thrombocytopenias (longer than 90 days) were noted in nine cases. There were two toxic deaths (one graft failure with veno-occlusive disease in group 1, one aspergillosis in group 2). Of the 22 patients in PR, 9 remained in PR, 1 died, 11 converted to CR, and 1 progressed rapidly after AT. The patient transplanted in early relapse went back to CR.

For the 35 patients undergoing autologous transplantation, the median survival is 41 months and the projected 5-year survival is 28.5% ± 15% (Fig 7). The median duration of response is 28 months, but the PFS curve shows no plateau, with the last relapse occurring at 45 months (Fig 5). The clinical outcome after autologous transplantation was not influenced by the response after HDM (CR *v* PR), the percentage of plasma cells in the reinfused marrow, the use of myeloablative conditioning regimen, or the interval between the first HDM and autologous transplantation (within or beyond 120 days). The survival and PFS curves are not significantly different between the 10 patients in group 1 and the 25 patients in group 2.

DISCUSSION

The objectives of this double-intensive therapy were to achieve a high cell mass reduction with the first course of HDM and to prolong the remission duration with the second course of high-dose therapy. This approach is usual in the management of acute myeloid leukemia but had never been used in MM. The CR and the response rates after the first HDM were 25% and 71%, respectively, which is comparable with results obtained previously.[2] The only

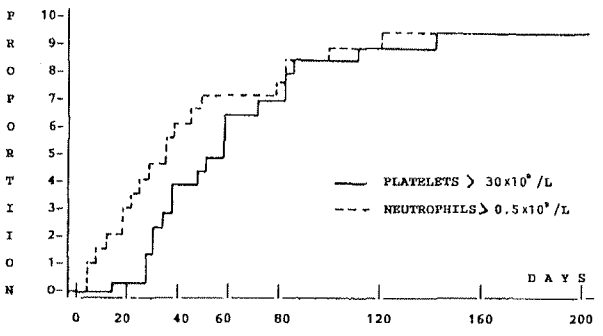

Fig 6. Duration of neutropenia and of thrombocytopenia after autologous transplantation.

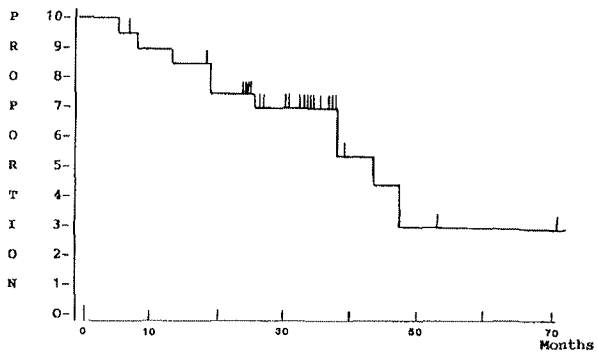

Fig 7. Survival of the 35 patients undergoing autologous transplantation.

parameter influencing the response rate was the age, with patients under the age of 50 achieving an 83% response rate versus 62% for older ones.

Despite the good cytoreduction obtained by the first course of HDM, the median survival was only 24 months for the entire group, 17 months in advanced MM, and 37 months in newly diagnosed patients. Age under 50 years and response to HDM were the only significant prognostic factors, while, as already noted after autologous transplantation, IgG MM appeared to have a slightly better prognosis.[15] In this multicenter study we could not confirm the prognostic impact of β2 microglobulin level. The overall response rate and survival did not differ significantly between advanced and newly diagnosed MM. As published previously,[15] the CR and response rate after HDM were satisfactory in primarily resistant MM and sensitive or untested relapses, but poor in the subgroup of resistant relapses. Therefore, this aggressive strategy could be a salvage therapy for sensitive relapses or primarily resistant MM. However, the myelosuppression induced by HDM given without any hematopoietic support was severe, leading to 8% toxic deaths. The median duration of neutropenia was longer in the group of heavily pretreated patients (29.5 days *v* 23 days) and it was not possible to correlate the duration of neutropenia to any pretreatment characteristic. Recombinant hematopoietic growth factors (interleukin-3 [IL-3], granulocyte-macrophage colony-stimulating factor [GM-CSF], or G-CSF) could stimulate marrow recovery after HDM.[16,17] In a preliminary study with GM-CSF, the duration of neutropenia was reduced in patients with adequate marrow reserve.[16] However, it has been shown that these growth factors can stimulate the in vitro proliferation of myeloma cells in synergy with IL-6.[18,19] Thus, the issues of safety and efficacy of GM-CSF after HDM are being addressed in an ongoing randomized study versus placebo.

Even if historical comparisons are not recommended, our results do not appear to be superior to those achieved with only one course of intensive therapy.[2,8,15,20] This could be partially explained by the fact that only 25% of patients with advanced MM and only 51% of patients with newly diagnosed MM had undergone the second course, mainly because of the toxicity of the first. However, the main cause of failure was relapse because the PFS curve of the 69

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